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Clinically Isolated Neurosarcoidosis: A Recommended Diagnostic Path

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Key Words
Neurosarcoidosis · Sarcoidosis · Magnetic resonance imaging · Spinal fluid analysis

Abstract
The involvement of the central nervous system in sarcoidosis can manifest with a variety of neurological symptoms, most of them nonspecific. We identified 13 patients with neurosarcoidosis diagnosed at our clinic. Six of 13 patients presented with clinically isolated neurosarcoidosis (CINS) without signs or symptoms of systemic disease. CINS patients were not different with respect to age, as well as imaging and spinal fluid findings, or disease course. However, we found spinal cord involvement in neurosarcoidosis patients much more common than previously described (in 8 out of 13 patients). Spinal cord affection was associated with older age at diagnosis and a less favorable response to therapy. Based on our findings, we propose a diagnostic path for neurosarcoidosis, including spinal magnetic resonance imaging (MRI) as a mandatory and early step during diagnostic workup.

Introduction

Sarcoidosis, a multisystem disease characterized by noncaseating granulomas predominantly affecting the lungs, is not uncommon in Northern European countries, with an annual incidence of 5–40 per 100,000 [1]. The etiology of sarcoidosis remains unknown, but an autoimmune reaction that is triggered by a pathogen (not yet known) in genetically predisposed individuals is the most likely cause. Neurosarcoidosis refers to disease manifestation of sarcoidosis within the nervous system. It is clinically apparent in 5–10% of patients, but has been demonstrated in up to 25% of sarcoidosis patients at autopsy [2–4]. The histopathological presentation of neurosarcoidosis is either the pathognomonic noncaseating granuloma with lymphomonuclear infiltrates and multinuclear macrophages, or an infiltration of inflammatory cells into the meninges or extracellular spaces causing microvascular damage and diffuse white matter lesions [5–7]. Neurological symptoms may range from basal meningitis with cranial nerve involvement to limb paralysis or seizures due to a granulomatous lesion or even slowly

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Table 1. Clinical characteristics of patients with neurosarcoidosis

Patient no./sex	Age, years	Neurological symptoms (presenting, y/n)	Systemic symptoms	cMRI	sMRI	LP	Treatment	Clinical course (follow up, m)
1/M**	35	Cranial neuritis (y)	+	+	n.d.	+	Steroids + MTX	better (40)
2/M**	49	Headache, focal seizure (n)	+	+	+	–	Steroids	stable (30)
3/M**	57	Meningitis, optic neuritis, headache, gait disturbance (n)	+	+	+	+	Steroids, steroids + MTX, steroids	worse (39)
4/F*	38	Headache, facial hypoesthesia (y)	+	+	–	+	Steroids, stopped after 24 m	better (41)
5/F**	46	Paraplegia (Myelitis) (n)	+	–	+	+	Steroids + MTX	died (37)
6/F**	27	Polyneuritis (y)	+	–	n.d.	+	None	better (33)
7/F***	31	Optic neuritis (y)	+	+	+	+	Steroids for 144 m, MTX monotherapy since 24 m	worse (169)
8/M**	48	Basal meningitis, radiculopathy (y)	–	+	+	+	2 Steroid courses for overall 7 m, stopped since 21 m	better (37)
9/F**	60	Slowly progressive tetraparesis (y)	–	–	+	–	Steroids + azathioprine	better (19)
10/M*	20	Basal meningitis (y)	–	+	n.d.	+	Steroids + mycophenolate	stable (204)
11/F**	38	Progressive left paresis/radiculitis (y)	–	–	+	+	Steroids 17 m, MTX 3 m stopped due to stabilization of disease, infliximab 3 m, MTX 13 m, Rituximab 6 m, tocilizumab 3 m, steroids	worse (62)
12/M**	52	Basal meningitis (y)	–	+	n.d.	+	Steroids	stable (2)
13/M**	51	Tetraparesis (y)	–	–	+	+	Steroids	stable (4)

Diagnostic certainty: Neurosarcoidosis possible*, probable**, certain***. + = Pathological findings; – = normal; n.d. = not done. cMRI = cranial MRI; sMRI = MRI of the spine; LP = lumbar puncture results; MTX = methotrexate; m = months.

progressive cognitive decline [8]. Due to the variability of symptoms, neurosarcoidosis is a diagnostic challenge. Furthermore, there are currently no unambiguous (imaging or laboratory) parameters to aid in the diagnosis.

We here report on 13 neurosarcoidosis cases from our institution with the typical manifold neurological symptomatology. Based on our experience, we recommend a diagnostic path to aid in identifying the disease.

Patients and Methods

We searched the clinical database of the Department of Neurology at the University Hospital Zurich for all patients that were seen with suspected neurosarcoidosis since 2000. All cases with a diagnostic certainty of at least 'possible neurosarcoidosis' [9] were included. 'Possible neurosarcoidosis' was defined as clinical condition and neurodiagnostic workup consistent with neurosarcoidosis, but without histological evidence. For 'probable neurosarcoidosis', typical laboratory findings including cerebrospinal fluid (CSF) abnormalities (elevated levels of CSF protein and/or cells, presence of oligoclonal bands) and/or histological evidence of systemic disease had to be present in addition to the clinical and neurodiagnostic findings compatible with neurosarcoidosis, while the diagnosis of 'definite neurosarcoidosis' required proof by a nervous system biopsy. Patient charts were reviewed and clinical characteristics, imaging findings, results of laboratory tests, as well as treatment and outcome were recorded. Comparisons between groups were done using a two-sided *t* test. Furthermore, a Medline search for 'spinal cord sarcoidosis' was performed and all studies from 1994 onwards reporting more than one case of spinal cord sarcoidosis were identified. All papers reporting clinical outcome or spinal cord MRI data were included for the analysis in table 3.

Results

Patient Characteristics

Thirteen patients were diagnosed with neurosarcoidosis between 2000 and 2014, of those 1 with possible, 11 with probable, and 1 with definite neurosarcoidosis. Patient characteristics are shown in table 1. The mean age at

Table 2. Imaging and spinal fluid/serum findings in patients with neurosarcoidosis

Criteria	CINS (n = 6)	Neurosarcoidosis with systemic signs (n = 7)
Age at diagnosis, years	44.8±14.1	40.4±10.7
Presenting symptoms neurological	6	4
Imaging findings (out of n)		
MRI: spinal	4 (4)	4 (4)
Meningeal enhancement	1	1
Solitary lesion (s)	1	1
T2/FLAIR- hyperintensities	2	2
MRI: cerebral	3 (6)	5 (7)
Meningeal enhancement	3	0
Solitary lesions (s)	0	2
T2/FLAIR- hyperintensities	0	3
MRI: spinal and cerebral findings	1	3
Positive chest X-ray	0	5
Spinal fluid findings (out of n)		
Increased cell count (/μl)	4 (6) (range 34–273)	2 (7) (range 10–76)
Increased protein (mg/l)	5 (6) (range 436–3,940)	4 (7) (range 506–2,600)
Glucose	2 decreased (6)	2 decreased, 1 increased (7)
Increased lactate	2 (6)	1 (7)
Positive oligoclonal bands	4 (6)	2 (5)
Positive IgG Index	3 (6)	3 (5)
Positive IgA Index	1 (6)	1 (5)
Positive IgM Index	0 (6)	1 (5)
Increased sIL2 receptor (pg/ml)	3 (6) (range 184–426)	1 (1) (439)
ACE elevation (serum)	0 (5)	1 (2)

the onset of neurological symptoms was 42.5 years (range 20–60 years), with a male:female ratio of close to 1:1. The median follow-up was 37 months. Seven patients displayed clinical signs of systemic sarcoidosis before or at the time of presentation for neurological workup, 6 with pulmonary disease and 1 with cardiac arrhythmia that led to further diagnostic workup and was attributed to sarcoidosis. Four of these 7 patients presented initially with neurological symptoms, but were diagnosed only after the occurrence of systemic signs. The remaining 6 patients were diagnosed only based on neurological symptoms (P8–13 in table 1), and will be referred to as clinically isolated neurosarcoidosis (CINS). CSF was abnormal in 12 of 13 cases with findings ranging from mild pleocytosis to substantial elevation in protein content, positive oligoclonal bands, and/or increased levels of soluble interleukin 2 receptor alpha chain (CD25) (tables 1 and 2).

Neuropathy was suspected in one patient who reported a tingling sensation in both lower legs. ENMG was unremarkable in this case. In two patients, one of them only several years after diagnosis of neurosarcoidosis and immunosuppressive treatment, ENMG revealed a beginning axonal peripheral neuropathy.

Except for one case (P6) with rapid spontaneous clinical improvement, all patients received immunosuppressive/anti-inflammatory therapies, either with steroids alone (P2, P4, P8, P12, P13) at an earlier stage of treatment with rather short follow-up: median 30 months; steroids in combination with methotrexate (MTX): P1, P3, P5 with a median follow-up of 39 months, or in combination with other drugs: azathioprine (P9), mycophenolate (P10), or monotherapy with MTX (P7). One patient with severe disease progression was switched from steroids to MTX and later to infliximab and tocilizumab, without achieving sufficient control of symptoms (P11). Overall, the clinical course was good (neurological signs/symptoms stable or better) in 9 patients and progressive (worsening of signs/symptoms) in 4; one patient died following long-term steroid therapy and immobilization.

Imaging Findings

MRI of the brain was abnormal in 8 cases and normal in 5. MRI of the spinal cord was pathological in 8 cases, not done in 4 cases and normal in only 1 patient (table 1). Both, spinal and cerebral imaging findings were present in 5 patients. Patients with spinal cord involvement tend-

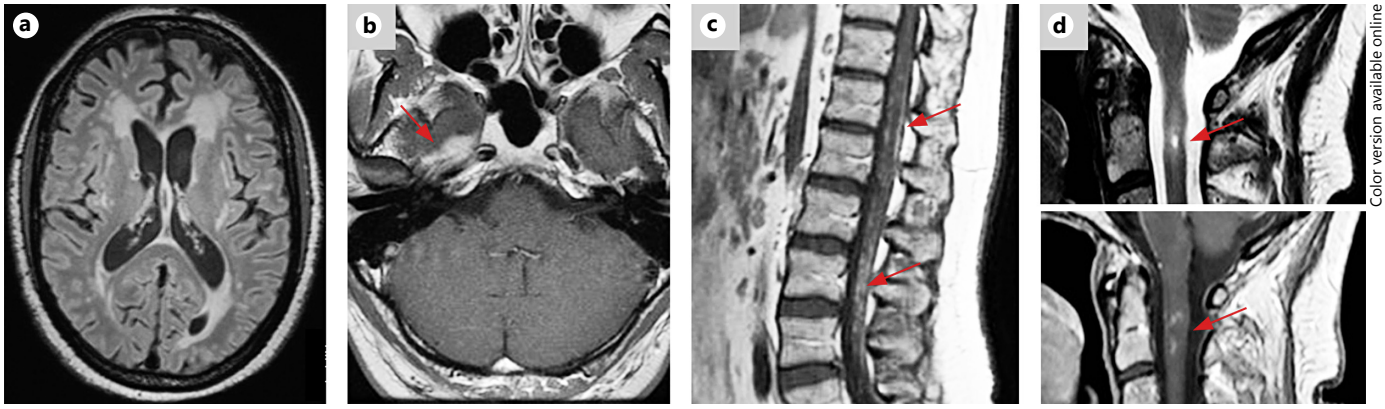

Fig. 1. Neurosarcoidosis imaging patterns. Characteristic MRI findings in neurosarcoidosis patients: (**a**) T2/ FLAIR hyperintensities without contrast enhancement, (**b**) brain solitary, contrast enhancing lesion (arrow), (**c**) meningeal and diffuse parenchymal contrast enhancement (arrows), and (**d**) spinal cord solitary contrast enhancing lesion (upper panel: T2w image, lower panel: T1 post contrast image).

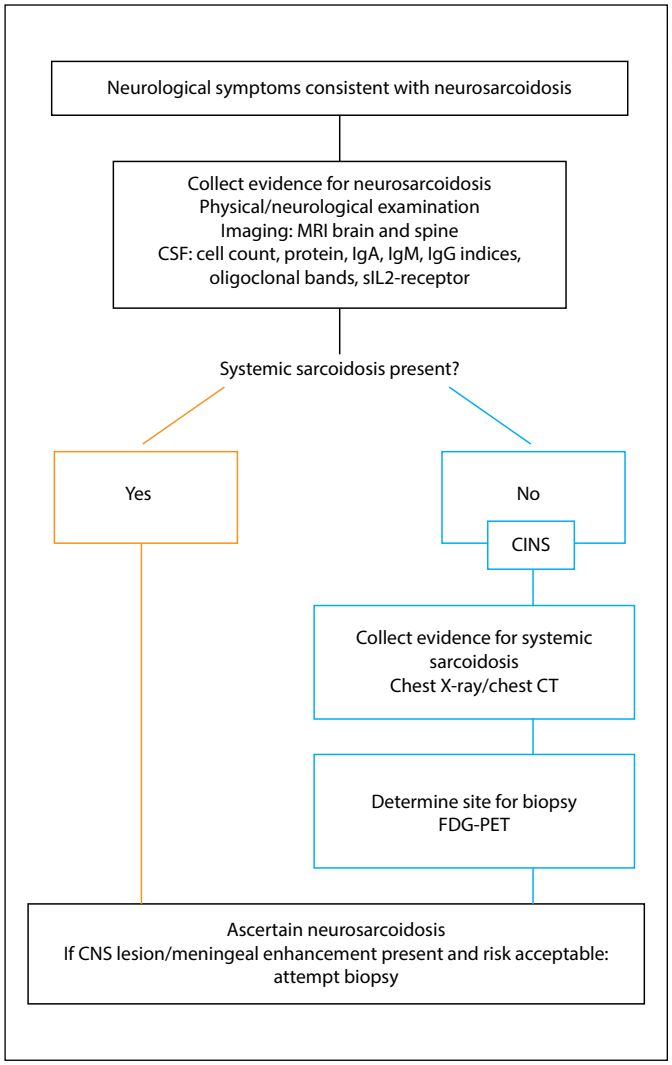

Fig. 2. Suggested diagnostic path for neurosarcoidosis.

ed to be older (48.8 ± 9.2 vs. 36.2 ± 5.1 years, p = 0.06) and had a less favorable response to therapy (p = 0.01).

We further classified MRI patterns of neurosarcoidosis into a) meningeal contrast enhancement, b) solitary lesions, or c) predominantly subcortical T2/FLAIR hyperintensities with nonspecific appearance (table 2 and fig. 1). These three patterns could be discerned on MRI of the brain as well as the spine. All of the solitary spinal lesions/T2 hyperintensities (n = 6) were located in the cervical or thoracic spine.

Chest X-ray did not show any abnormalities in patients with CINS, but was positive in 5 out of the remaining 7 patients with systemic symptoms (table 2). In 4 out of the 6 CINS patients, FDG-PET was performed to search for a biopsy site, which was successful in all 4. In 3 of these patients, the histological confirmation of sarcoidosis was based on biopsy results from FDG-enhancing sites revealed by PET.

Discussion

To reach the diagnosis of definite or at least probable neurosarcoidosis, a biopsy must be obtained to demonstrate the typical histological picture of sarcoidosis either in the nervous system (definite) or another affected organ along with imaging and laboratory signs suggestive of neurosarcoidosis (probable neurosarcoidosis). In patients with known systemic sarcoidosis and neurological symptoms that remain otherwise unexplained, the suspicion of neurosarcoidosis is high. The diagnostic path for this scenario is focused on the collection of evidence for CNS involvement by clinical examination, MRI, and CSF studies (fig. 2). It is now established that neither serum

Table 3. Summary of studies reporting spinal cord affection in neurosarcoidosis

Study	Spinal cord affection of neurosarcoidosis patients, n/n (%)	Spinal cord level affected, n	Outcome, n
Christoforidis et al. [27], 1999	8/38 (21)	4 cervical; 1 thoracic; 3 lumbal	3 improved; 4 stable or worse; 1 unknown
Joseph and Scolding [28], 2008	5/30 (17)	–	5 worse
Lexa et al. [29], 1994	4/24 (17)	–	4 stable/improved radiologically (no clinical outcome reported)
Marangoni et al. [11], 2006	3/7 (43)	2 cervical; 1 thoracic	2 improved; 1 worse/died
Nozaki et al. [7], 2012	17/70 (24)	17 with positive spinal MRI (affected levels not reported)	–
Sakushima et al. [21], 2011	6/17 (35)	6 cervical	3 stable/improved; 3 worse
Sharma [30], 1997	1/38 (3)	all segments	1 improved
Spencer et al. [31], 2004	9/21 (43)	8 cervical; 1 thoracic	7 improved; 2 worse
Zajicek et al. [9], 1999	19/68 (28)	11 with positive spinal MRI (affected levels not reported)	6 stable/improved; 13 worse
Reports of selected cases with spinal cord sarcoidosis			
Cohen-Aubart et al. [32], 2010	31/31 (100)	15 cervical; 17 thoracic; 6 lumbosacral	11 improved; 17 worse; 3 unknown
Kobayashi et al. [33], 2013	9/9 (100)	4 cervical; 3 thoracic; 1 lumbar; 1 all segments	8 improved; 1 stable
Saleh et al. [34], 2006	8 (100) retrospective	4 cervical; 4 thoracic	6 improved; 2 worse
Sohn et al. [20], 2014	27/27 (100)	21 cervical; 18 thoracic; 10 lumbosacral	–
Varron et al. [23], 2009	7/7 (100)	4 cervical; 2 lumbosacral; 1 whole spinal cord	3 stable; 1 improved; 1 worse; 2 unknown

Not reported: '–'.

nor spinal fluid angiotensin converting enzyme (ACE) levels are helpful for the diagnosis of neurosarcoidosis (sensitivity of 24–55% for CSF levels) [10, 11]. CSF analysis should include glucose, lactate, protein, number and types of cells and antibody indices (IgM, IgA, IgG) since these parameters may correlate with disease activity [12]. However, depending on the MRI-defined disease extension (e.g., diffuse leptomeningeal enhancement versus solitary lesions) and disease activity, CSF parameters might be normal in approximately 40% of cases [12]. Oligoclonal bands were positive only in 22% of cases with probable or definite neurosarcoidosis [12]. Spinal fluid quantification of soluble CSF interleukin 2 receptor alpha chain, a marker of T-cell activation, appears suitable in the diagnostic workup for neurosarcoidosis, since levels above 150 pg/ml allow to discriminate neurosarcoidosis from other differential diagnoses such as multiple sclerosis and vasculitis as well as healthy controls with an overall accuracy of 93% (sensitivity of 61% and specificity of 93%) [13]. While activated CD4+ T- cells are the hallmark of the sarcoid granuloma immunopathogenesis and the CD4/CD8 T-cell ratio typically increased in bronchoalveolar lavage of sarcoidosis patients, the diagnostic utility of this test for neurosarcoidosis remains uncertain. In a previous case series of 8 patients, it was increased only in three and normal in five [14–16]. Sarcoid-induced neuropathy is rare, but may be a presenting symptom of neurosarcoidosis [3, 17–19]. ENMG, albeit not specific for neurosarcoidosis, is certainly of value in cases in which symptoms of neuropathy or myopathy are reported and

for diagnosis and follow up of therapy-induced myopathy or neuropathy. Besides the above-mentioned diagnostic parameters, neuroimaging with MRI remains an essential part of the diagnostic workup for neurosarcoidosis. The MRI protocol should include high resolution T2 and FLAIR images for detection of edema or white matter changes, as well as pre- and post-contrast T1, to reveal even subtle meningeal contrast enhancement. To discriminate vascular pathologies or microbleeds, MRA and susceptibility-weighted (T2*) imaging should also be performed.

The prevalence of spinal cord lesions on MRI in our patient cohort was high (62%). Previous reports estimated the prevalence of spinal cord neurosarcoidosis to be about 1% of all sarcoidosis patients, or between 3 and 43% of neurosarcoidosis patients (table 3) [20–22]. We assume that spinal cord involvement is often missed, either due to unspecific symptoms that might be related to cord involvement such as sensory disturbances or because it was clinically silent. The cervical spine is most frequently affected; however, all spinal cord levels may reveal disease activity (table 3). Identification of spinal cord involvement is important, since it might indicate patients with a more protracted disease course requiring earlier start of nonsteroidal therapies [21, 23, 24]. While our case series supports a more unfavorable clinical course when the spinal cord is affected, it is interesting to note that clinical outcome data of previous studies in this subgroup of patients are actually less clear (table 3). Due to the significant prevalence of spinal cord involvement, we suggest that spinal MRI should be included in the routine workup of neurosarcoidosis. Since the course of treatment may last for prolonged periods of time, imaging evidence of disease activity is highly important and can also monitor treatment efficacy. A CNS biopsy should be undertaken to clear all doubts, if any.

Due to the rarity of the disease and the small sample size of this retrospective study, interpretation of our findings is limited. However, based on our experience, we suggest the following diagnostic path for patients with suspected neurosarcoidosis.

In the case of a patient presenting with neurological symptoms consistent with neurosarcoidosis, but no further clinical evidence of systemic sarcoidosis (fig. 2, right side), searching for systemic disease manifestations is the first step. One aspect is that subclinical systemic disease should be recognized; another is that a biopsy site might be found. Routine workup for systemic involvement should include a chest-CT scan, and, if doubts remain, [18F]-fluorodeoxyglucose-positron emission tomography, as it might be more sensitive to reveal a suspicious lymph node that is accessible at minimal procedural risk [25, 26].

Disclosure Statement

The authors have no conflict of interest to disclose.

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